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Abstract: BACKGROUND: Community-acquired pneumonia (CAP) is common and associated with a considerable risk of acute kidney injury (AKI). METHODS: We prospectively enrolled 341 patients presenting to the emergency department with CAP (mean age 72, male 61%). Blinded measurements of three natriuretic peptides (NT-proBNP, MR-proANP and BNP) were performed upon presentation. The primary endpoint was the accuracy of the natriuretic peptides to predict AKI within 48h. RESULTS: AKI occurred in 24 patients (7.6%) within the first 48h. NPs and creatinine were significantly higher in AKI compared with patients without AKI (NT-proBNP 9517 [2042-26,792] vs 1177 [280-4167]pg/ml; MR-proANP 641 [196-1075] vs 182 [99-352]pmol/l; BNP 592 [230-1630] vs 160 [64-463]pg/ml; creatinine 166 [131-289] versus 100 [78-134] mol/l, $P < 0.001$ for each). Predictive accuracy as quantified by the area under the receiver operating characteristics curve was moderate to high: NT-proBNP 0.79 (95%CI 0.70-0.88), MR-proANP 0.78 (95%CI 0.67-0.88), BNP 0.74 (95%CI 0.63-0.85), creatinine 0.77 (95%CI 0.66-0.88). In multivariate logistic regression analysis, NPs remained the only independent AKI predictors: NT-proBNP (increase of 200pg/ml) OR=1.01, 95%CI 1.00-1.01, $P=0.009$; MR-proANP (increase of 100pg/ml) OR=1.23, 95%CI 1.09-1.39, $P=0.001$; BNP (increase of 100pg/ml) OR=1.08, 95%CI 1.03-1.14, $P=0.002$. CONCLUSIONS: NP levels are significantly elevated in CAP-patients experiencing early AKI. Their potential to predict early AKI is comparable to serum creatinine and might be useful in cases of diagnostic uncertainty.

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Natriuretic peptides for early prediction of acute kidney injury in community-acquired pneumonia

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Abbreviations. CAP, community-acquired pneumonia; AKI, acute kidney injury; NP, natriuretic peptide; NT-proBNP, N-terminal pro B-type natriuretic peptide; MR-proANP, mid-regional pro-atrial natriuretic peptide; BNP, B-type natriuretic peptide; HIV, human immunodeficiency virus; ED, emergency department; AKIN, Acute Kidney Injury Network classification; PSI, pneumonia severity index; CURB-65, confusion, urea plasma level, respiratory rate, blood pressure, age over 65 years; EDTA, ethylenediaminetetraacetic acid; AUC, area under the curve; CKD, chronic kidney disease; CRP, C-reactive protein; ROC, receiver operating characteristic; CI, confidence interval; HR, hazard ratio; OR, odds ratio; TNF, tumor necrosis factor; IL, interleukin; mRNA, messenger ribonucleic acid; proANP, pro-atrial natriuretic peptide.

Abstract

Background: Community-acquired pneumonia (CAP) is common and associated with a considerable risk of acute kidney injury (AKI).

Methods. We prospectively enrolled 341 patients presenting to the emergency department with CAP (mean age 72, male 61%). Blinded measurements of three natriuretic peptides (NT-proBNP, MR-proANP and BNP) were performed upon presentation. The primary endpoint was the accuracy of the natriuretic peptides to predict AKI within 48 hours.

Results. AKI occurred in 24 patients (7.6%) within the first 48 hours. NPs and creatinine were significantly higher in AKI compared with patients without AKI (NT-proBNP 9517 [2042-26792] vs 1177 [280-4167] pg/ml; MR-proANP 641 [196-1075] vs 182 [99-352] pmol/l; BNP 592 [230-1630] vs 160 [64-463] pg/ml; creatinine 166 [131-289] versus 100 [78-134] μ mol/L, $P < 0.001$ for each). Predictive accuracy as quantified by the area under the receiver operating characteristics curve was moderate to high: NT-proBNP 0.79 (95%CI 0.70-0.88), MR-proANP 0.78 (95%CI 0.67-0.88), BNP 0.74 (95%CI 0.63-0.85), creatinine 0.77 (95%CI 0.66-0.88). In multivariate logistic regression analysis, NPs remained the only independent AKI predictors: NT-proBNP (increase of 200 pg/ml) OR=1.01, 95%CI 1.00-1.01, $P=0.009$; MR-proANP (increase of 100 pg/ml) OR=1.23, 95%CI 1.09-1.39, $P=0.001$; BNP (increase of 100 pg/ml) OR=1.08, 95%CI 1.03-1.14, $P=0.002$.

Conclusions. NP levels are significantly elevated in CAP-patients experiencing early AKI. Their potential to predict early AKI is comparable to serum creatinine and might be useful in cases of diagnostic uncertainty.

Keywords: acute renal failure, natriuretic peptides, community-acquired pneumonia.

Highlights

- Community-acquired pneumonia (CAP) is associated with a considerable risk of acute kidney injury (AKI)
- We prospectively enrolled 341 patients presenting to the emergency department with CAP
- Natriuretic peptides were accurate predictors of early in-hospital AKI
- Due to the high incidence of CAP and the prognostic importance of CAP-associated AKI, its early recognition is of great clinical importance.

1. Introduction

Community-acquired pneumonia (CAP) is a common infectious cause of hospitalization in developed countries. Between 1998 and 2002, CAP was the primary reason for 5.8% of all United States Medicare hospitalizations and contributed to almost 10% of in-hospital stays [1]. CAP-associated AKI is of great clinical importance: CAP patients suffering from AKI are more likely to require medical intensive care, have longer hospital stays and suffer from increased in-hospital and long-term mortality [2, 3]. Hence, a rapid and reliable predictor of AKI might help physicians in the early identification of patients requiring closer monitoring and possibly benefiting from adequate hydration and avoidance of nephrotoxic treatments. Importantly, sepsis-induced AKI appears to have a distinct pathophysiology and identity, with the extent of cardiac stress and inflammation acting as primary triggers [4].

Natriuretic peptides (NPs), a family of ring-shaped vasoactive hormones with considerable sequence homology, have repeatedly been shown to be increased in salt- and water-retaining states, such as heart failure or AKI, in an attempt to overcome the salt and water retention via their natriuretic and diuretic properties [5, 6]. Their levels have consistently been shown to mirror the extent of cardiac stress in various disease states [5, 6]. Additionally, pro-inflammatory cytokines and the activation of the sympathetic nervous system have recently been identified as triggers of NP secretion [7].

Consequently, NP levels may integrate the severity of cardiac stress and the inflammatory cytokine response as important triggers of sepsis-induced AKI. Therefore, we aimed to evaluate and directly compare the potential of three NPs to predict the occurrence of AKI in patients with CAP.

2. Materials and Methods

This study specifically investigated the potential of plasma NT-proBNP, MR-proANP and BNP levels to predict early AKI in hospitalised patients with CAP. We screened 422 consecutive patients presenting with suspected CAP from November 2003 to March 2007 for enrolment into this study [8-10]. Due to lack of resources, recruitment was interrupted from February 2005 to April 2006. The study was carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committee. Written informed consent was obtained from all participating patients.

2.1. Setting and study population

To be eligible for enrolment into the trial, patients had to be over 18 years old and be able to give a written consent. Consecutive CAP patients were asked to participate in the study and to give informed consent shortly after presentation to the hospital. Patients with cystic fibrosis, active pulmonary tuberculosis, hospital-acquired pneumonia, severely immunocompromized patients (HIV, active chemotherapy, solid organ transplant, on methotrexate, azathioprine, cyclosporin, or anti-tumor necrosis factor- α) and patients undergoing chronic dialysis were excluded. Community-acquired pneumonia was defined as a new infiltrate on chest radiograph and history consistent with pneumonia with 3 or more of the following newly acquired features: cough, sputum production, dyspnea, core body temperature exceeding 38.0°C, auscultatory findings of abnormal breath sounds and rales, and leukocyte count greater than 10×10^9 or less than 4×10^9 cells L^{-1} [11]. CAP was confirmed after review of all medical records pertaining to the patients at a follow-up clinic review. No single biomarker or pre-specified biomarker level was necessary for the diagnosis of CAP.

Similarly, the initiation of antibiotic therapy was not necessary for the diagnosis of CAP.

2.2. Site of care

Patients presented either as general practitioner referrals or as self-referrals to the ED. Patients were examined on presentation to the emergency department by a resident supervised by a board-certified specialist in internal medicine. The choice of antibiotic regimen was left to the discretion of the treating physician and was made in accordance with locally-approved antimicrobial guidelines. The exact antibiotic regimen and treatment duration as well as results of microbiology testing were documented. Antibiotic treatment was defined as appropriate if the agent was chosen in accordance with locally-approved guidelines and the antibiotics initially chosen covered the microorganisms obtained from microbiology studies. In the case of negative microbiology results, antibiotic treatment was defined as appropriate if the regimen was chosen in accordance with the guidelines. Antibiotic treatment was defined as inappropriate if the choice of regimen was not in accordance with the guidelines or if the antibiotic agent initially chosen did not cover the microorganisms obtained from the microbiology studies. The study investigators were neither directly involved in patient care in the ED nor did they have any influence on the decision to discharge patients from the ward.

2.3. Study protocol

All patients were subject to an initial clinical assessment including medical history, physical examination, electrocardiography, pulse oximetry, blood tests including

arterial blood gas analysis (when indicated) and chest x-ray. Demographics and co-morbidities including the presence of chronic kidney disease were recorded on the ED upon arrival. The medical history was recorded from patient history, documentation of prior admissions and completed using general practitioners' documentation.

Long-term survival was assessed during a one-time telephone contact. If the patient could not be contacted, family members, general practitioners and the local registry office were contacted to confirm the survival status of the patient.

2.4. Renal failure and severity of illness

We defined AKI according to the Acute Kidney Injury Network (AKIN) classification as an in-hospital increase in creatinine greater than 26.4 $\mu\text{mol/l}$ (0.3mg/dl) occurring during the first 48 hours, which persisted after adequate volume resuscitation [12]. The potential of presentation NP levels to predict early AKI was assessed as the primary endpoint.

PSI is a clinical prediction index used to calculate the probability of mortality among patients with CAP. The rule uses demographics, co-morbid illnesses, findings on physical examination, vital signs and laboratory findings. PSI allows stratification into five risk categories [13]. CURB-65 is another morbidity prediction index. The score is an acronym for each of the risk factors measured: confusion, urea plasma level, respiratory rate, blood pressure and age over 65 years. Each risk factor scores one point, for a maximum score of 5 [14].

2.5. Measurements of MR-proANP, NT-proBNP and BNP

At presentation to the ED, blood samples were collected into bottles containing potassium EDTA. After centrifugation samples were immediately frozen at -80°C

until later analysis. Plasma biomarker concentrations were measured in a blinded fashion. Detection of MR-proANP was performed using a sandwich immunoassay (MR-proANP LIA, B.R.A.H.M.S, Hennigsdorf / Berlin, Germany). NT-proBNP levels were determined by a quantitative electrochemiluminescence immunoassay (Elecsys proBNP; Roche Diagnostics AG, Zug, Switzerland). BNP was detected in EDTA plasma with a fluorescence immunoassay (Biosite Diagnostics, La Jolla, CA, USA). The serial creatinine measurements were performed with the chromogenic Jaffe's reaction.

2.6. Statistical analyses

Categorical variables are expressed as counts (percentage) and continuous variables as median and interquartile ranges. Correlation analyses were performed using Spearman rank correlation. Comparisons between variables and outcome were made using the Student *t*-test, the Kruskal–Wallis test, the Mann–Whitney *U*-test and the chi-squared test as appropriate. AUC were compared using MedCalc software (version 9.2.; MedCalc Software, Mariakerke, Belgium). The potential of NP levels at presentation to predict AKI was assessed as the endpoint. To estimate the potential clinical relevance of biomarker measurements we used logistic regression models. We evaluated the incremental value of NPs to traditional AKI predictors. As traditional parameters, we defined a base set consisting of serum creatinine, pre-existing renal disease and pneumonia severity expressed in PSI points. These variables have been associated with AKI and mortality in patients with pneumonia in previous studies [2] and were significantly different in the patients group with AKI versus without AKI in this cohort. We then compared the performance of the base set alone with its performance after adding the NPs. Statistical analyses were performed using

SPSS/PC (version 19.0; SPSS Inc., Chicago, IL, USA) software package. A statistical significance level of 0.05 was used. All hypothesis testing was two-tailed.

3. Results

3.1. Baseline characteristics and clinical outcome:

A total of 422 patients were enrolled in this study. Baseline values from all three NPs were available for 341 of the 422 consecutive patients. These 341 patients constituted the study population included in analysis. The baseline characteristics and antibiotic treatment of the study population are displayed in Table 1. The median follow-up time was 942 days [366-1626]. In-hospital and long-term follow-up were complete in 100% of the patients. We also assessed the predictive potential of NPs for short- and long-term mortality and describe the results elsewhere [15].

The mean age was 72 years and there were 209 men (61%). Overall, 24 (7.6%) patients developed AKI during the first 48 hours of the index hospitalisation. Of these 24 patients, 5 required renal replacement therapy (RRT) during the index hospitalisation. There were no differences in patients with AKI versus without AKI in respect to gender, vital signs, antibiotic treatment, its appropriateness and antibiotic class. Patients with known CKD, hypertensive heart disease and older patients developed AKI more frequently. AKI was associated with short- and long-term mortality (44% non-AKI vs. 67% AKI patients died) (Table 1).

3.2. Plasma NP levels in patients experiencing acute kidney injury:

NP levels in this cohort of CAP patients correlated significantly with disease severity classified by pneumonia severity index (PSI) points (NT-proBNP: $r=0.532$, $P<0.001$; MR-proANP: $r=0.567$, $P<0.001$; BNP: $r=0.467$, $P<0.001$). Patients experiencing early AKI suffered more severe CAP according to PSI points (Table 1). The highest presentation levels of NPs were observed in early AKI patients subsequently requiring RRT, the lowest in patients without early AKI. Figure 1 shows presentation NT-proBNP levels as an example. For MR-proANP the medians were 182 [99-352]

pmol/l without AKI, 478 [156-475] pmol/l in AKI without RRT requirement; 2400 [761-2495] pmol/l in AKI with RRT requirement, $P<0.001$; for BNP the medians were 160 [64-463] pg/ml without AKI, 436 [197-1629] pg/ml with AKI without RRT, 1427 [592-5311] pg/ml in AKI with RRT requirement, $P<0.001$).

While a weak albeit significant correlation also existed between PSI point values CRP levels ($r=0.113$, $P=0.04$) and leukocyte count ($r=0.122$, $P=0.03$), there was no difference in these markers between AKI and non-AKI patients (leukocyte count $P=0.9$; CRP $P=0.67$).

3.3. Predictors of acute kidney injury

To evaluate the potential of serum creatinine and the NP measurements at presentation to predict the occurrence of AKI, receiver operating characteristic (ROC) analyses were performed. The area under the ROC curve (AUC) for the prediction of AKI of NT-proBNP, MR-proANP and BNP was comparable to creatinine, as shown in Figure 2 and Table 3A.

It must be noted that the predictive accuracy for AKI was consistent even after exclusion of 39 patients with a history of congestive heart failure (AUC NT-proBNP: 0.79; 95%CI 0.69-0.89; AUC MR-proANP: 0.79; 95%CI 0.70-0.90; AUC BNP: 0.74; 95%CI 0.63-0.86).

We defined a base set of traditional parameters as consisting of serum creatinine, chronic kidney disease and pneumonia severity expressed in PSI. When entering these traditional parameters and the NPs into a univariate regression analysis, all the variables were predictive for AKI (Table 2). The antibiotic treatment and its appropriateness were not protective against AKI, as assessed by univariate logistic regression analysis.

To assess a possible incremental value of the NPs to the traditional predictive parameters, multivariate regression analysis was performed. We compared the performance of the base set alone with its performance after adding the NPs using ROC plot analysis (Table 3B). The AUC for base set alone was not significantly different after adding one of the three NPs.

As a next step, we compared the accuracy of a three NPs model with the accuracy of single base set predictors (Table 3C). The AUC for the three NPs model was significantly larger than the AUCs for the clinical parameters CKD and pneumonia severity respectively. Furthermore, the AUC for the three NPs tended to be larger than for serum creatinine.

After inclusion of the base set variables and one of the NPs in a multivariate regression, only the NP remained a significant AKI predictor (Table 2). Using the other two NPs in the same model, the predictive potential for MR-proANP [increase of 100 pmol/L] was HR 1.23, 95%CI 1.09-1.39, $P=0.001$; for BNP [increase of 100 pmol/L]: HR 1.08, 95%CI 1.03-1.14, $P=0.002$).

After exclusion of 38 patients with a history of congestive heart failure, the predictive ability of NPs remained consistent (NT-proBNP [for an increase of 200 pg/ml]: OR 1.01, 95%CI 1.00-1.01, $P=0.02$; MR-proANP [for an increase of 100 pmol/L]: OR 1.27, 95%CI 1.12-1.45, $P<0.001$; BNP [for an increase of 100 pg/ml]: OR 1.09, 95%CI 1.03-1.15, $P=0.004$).

4. Discussion

In this study, we examined the possible merit of plasma NP levels at presentation for the prediction of early AKI in 341 CAP patients. There are several key findings in this study. Firstly, NP levels at presentation were significantly higher in patients experiencing early AKI compared to non-AKI patients. Among the AKI patients, the highest NP levels were observed in patients who needed RRT in the course of hospitalization. Secondly, NP levels at presentation accurately predicted in-hospital AKI within the first 48 hours. Thirdly, the predictive potential of NP levels were independent of creatinine values at presentation and persisted after the exclusion of patients with a history of congestive heart failure.

Our results represent the first large-scale study investigating the potential of plasma NPs for the prediction of AKI in the setting of CAP. This confirms and further extends our previous findings that NP levels at presentation powerfully predict mortality for CAP patients [15-17]. Infection-induced AKI has recently been proposed to be triggered by distinctly different pathophysiological patterns from non-infectious AKI. A recent study enrolling over 120 000 critically ill patients found that patients suffering from sepsis-induced AKI display more pronounced signs of cardiac stress, inflammation, renal and pulmonary impairment and disease acuity [4] compared to patients suffering from AKI of other causes.

NPs are vasoactive hormones that have consistently been shown to mirror the extent of cardiac stress and strain [5, 6]. Consequently, the assessment of NPs has become a cornerstone in the management of heart failure patients [18-20] and is endorsed by heart failure guidelines [21]. While CAP patients do not display the overt clinical picture of heart failure characterised by fluid retention and inadequate perfusion of peripheral organs, CAP is a significant stressor to the cardiovascular system through low peripheral vascular resistance, increased cardiac output and the occurrence of

arterio-venous shunts in inflamed areas [22]. Additionally, cardio-depressing effects have been described for pro-inflammatory mediators such as lipopolysaccharides [23], TNF- α and IL-1 β [24, 25]. Hence, elevated NP levels in the setting of CAP appear to identify a patient subgroup with limited cardiac reserves. Increased cardiac stress propels these patients over the threshold at which elevated cardiac output and adequate renal oxygen supply can be maintained and peripheral vasoconstriction leading to low local renal perfusion and AKI occurs. By reflecting cardio-renal interactions, NP levels mirror derangements in an important pathophysiological pathway to inflammatory AKI. This type of cardio-renal interaction in which a systemic non-cardiac, non-renal condition affects both organs was recently termed the cardio-renal syndrome Type 5 [26]. Supporting this hypothesis, another study with CAP patients and acute renal injury demonstrated an elevated neutrophil gelatinase-associated lipocain (NGAL) as a marker of acute reno-tubular damage and simultaneously elevated natriuretic peptide levels as a marker of cardiac stress [27]. A further reason for elevated NP levels in CAP is their response to inflammatory stimuli. A small study enrolling septic patients found NP levels to positively correlate with CRP values while finding no correlation between systolic dysfunction measured by echocardiography and NP levels [28]. Moreover, pro-inflammatory cytokines such as IL-1 β , IL-6 and TNF α have been shown to induce NP secretion from cultured myocytes *in vitro* [7, 29]. Concordantly, bacterial endotoxin was found to directly increase the expression of BNP mRNA in rat myocytes [30]. Thus NP levels appear to reflect the extent of systemic inflammation in CAP - an additional contributor to the pathogenesis of sepsis-induced AKI.

Additionally, NP levels reflect the extent of relevant co-morbidities, especially renal dysfunction. As it is the case in our study, NP levels are consistently negatively correlated with kidney function [31]. As in our study, impaired baseline renal function

has repeatedly been associated with an increased risk of AKI in various settings [4, 32]. However, besides purely reflecting baseline renal function, circulating NP levels might even be directly triggered by AKI. One older study examining 120 patients with differing degrees of renal impairment found urinary proANP levels to dramatically increase even before serum creatinine levels started to rise [33]. However, further studies concerning this observation are lacking. Hence, by integrating cardiac stress, inflammation and co-morbid burden of CAP patients, NP levels adequately predict early AKI with similar accuracy to serum creatinine.

Due to the high incidence of CAP and the prognostic importance of CAP-associated AKI, early AKI recognition is of great clinical importance. By adequately predicting the occurrence of AKI, NPs could provide physicians with a “red flag” for the early initiation of renoprotective interventions: maintaining positive fluid balance, preventing contrast-induced nephropathy, avoiding any nephrotoxic drugs and pentastarch fluid resuscitation [34] and adjusting medication doses to renal function. Additionally, initial studies indicate that treatment options may become available to reverse AKI if promptly initiated [35]. Finally, early recognition of AKI might lead to a more timely involvement of the nephrology care team, which has been associated with improved patient outcome in intensive care unit patients developing acute renal failure [36].

Several limitations merit consideration. First, this was a single center study. However, as baseline characteristics and mortality rates were similar to those of previous studies, we consider our results representative. Second, the incidence of AKI observed in our study was lower than observed in previous studies examining CAP patients [2, 3]. However, these studies either selectively evaluated community-acquired AKI, which can easily be detected by serum creatinine measurements at presentation, or examined the prevalence of AKI in critically ill patients. The inclusion

of unselected CAP patients presenting to the emergency department and the observational period of 48 hours explain the lower AKI incidence in our study. In fact, a similar study assessing early AKI occurring within the first 72 hours after presentation to the emergency department found a comparable AKI incidence [37]. Third, treating physicians were blinded to the NP test results. We cannot therefore assess the impact of an NP guided treatment strategy on AKI rate and long-term outcome. To ascertain blinded measurements of NP levels, all samples had to be stored until after the conduction of the study. However, we feel that blinded NP measurements were necessary to rule out a treatment bias. Fourth, the different NPs display significantly different long-term stability during storage at -80°C, with NT-proBNP and MR-proANP showing better stability than BNP [38]. As all samples were stored at -80° C until blinded batch analysis, we feel that the small trend towards predictive inferiority observed for BNP was probably caused by degradation of the detectable peptide during storage.

In conclusion, natriuretic peptide levels are significantly elevated in CAP patients experiencing early AKI. Their potential to predict early AKI is comparable to serum creatinine and might be useful in cases of diagnostic uncertainty.

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References

- [1] Fry AM, Shay DK, Holman RC, Curns AT, Anderson LJ. Trends in hospitalizations for pneumonia among persons aged 65 years or older in the United States, 1988-2002. *JAMA* 2005; 294:2712-2719.
- [2] Murugan R, Karajala-Subramanyam V, Lee M, et al. Acute kidney injury in non-severe pneumonia is associated with an increased immune response and lower survival. *Kidney Int* 2010; 77:527-535.
- [3] Akram AR, Singanayagam A, Choudhury G, Mandal P, Chalmers JD, Hill AT. Incidence and prognostic implications of acute kidney injury on admission in patients with community-acquired pneumonia. *Chest* 2010; 138:825-832.
- [4] Bagshaw SM, George C, Bellomo R. Early acute kidney injury and sepsis: a multicentre evaluation. *Crit Care* 2008; 12:R47.
- [5] Daniels LB, Maisel AS. Natriuretic peptides. *J Am Coll Cardiol* 2007; 50:2357-2368.
- [6] Mueller C, Breidthardt T, Laule-Kilian K, Christ M, Perruchoud AP. The integration of BNP and NT-proBNP into clinical medicine. *Swiss Med Wkly* 2007; 137:4-12.
- [7] Weinfeld MS, Chertow GM, Stevenson LW. Aggravated renal dysfunction during intensive therapy for advanced chronic heart failure. *Am Heart J* 1999; 138:285-290.
- [8] Mueller C, Laule-Kilian K, Frana B, et al. The use of B-type natriuretic peptide in the management of elderly patients with acute dyspnoea. *J Intern Med* 2005; 258:77-85.
- [9] Christ-Crain M, Stolz D, Bingisser R, et al. Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a randomized trial. *Am J Respir Crit Care Med* 2006; 174:84-93.

- [10] Potocki M, Breidhardt T, Reichlin T, et al. Midregional pro-adrenomedullin in addition to b-type natriuretic peptides in the risk stratification of patients with acute dyspnea: an observational study. *Crit Care* 2009; 13:R122.
- [11] Niederman MS, Mandell LA, Anzueto A, et al. Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. *Am J Respir Crit Care Med* 2001; 163:1730-1754.
- [12] Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007; 11:R31.
- [13] Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med* 1997; 336:243-250.
- [14] Lim WS, van der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax* 2003; 58:377-382.
- [15] Nowak A, Breidhardt T, Christ-Crain M, et al. Direct comparison of three natriuretic peptides for prediction of short- and long-term mortality in patients with community-acquired pneumonia. *Chest* 2012; 141:974-982.
- [16] Mueller C, Laule-Kilian K, Scholer A, Perruchoud AP. B-type natriuretic peptide for risk stratification in community-acquired pneumonia. *J Intern Med* 2005; 258:391-393.
- [17] Christ-Crain M, Breidhardt T, Stolz D, et al. Use of B-type natriuretic peptide in the risk stratification of community-acquired pneumonia. *J Intern Med* 2008; 264:166-176.
- [18] Maisel A, Mueller C, Nowak R, et al. Mid-region pro-hormone markers for diagnosis and prognosis in acute dyspnea: results from the BACH (Biomarkers in Acute Heart Failure) trial. *J Am Coll Cardiol* 2010; 55:2062-2076.

- [19] Porapakkham P, Zimmet H, Billah B, Krum H. B-type natriuretic peptide-guided heart failure therapy: A meta-analysis. *Arch Intern Med* 2010; 170:507-514.
- [20] Breidhardt T, Laule K, Strohmeyer AH, et al. Medical and economic long-term effects of B-type natriuretic peptide testing in patients with acute dyspnea. *Clin Chem* 2007; 53:1415-1422.
- [21] Pfister R, Schneider CA. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: application of natriuretic peptides. *Eur Heart J* 2009; 30:382-383; author reply 383.
- [22] Ince C. The microcirculation is the motor of sepsis. *Crit Care* 2005; 9 Suppl 4:S13-19.
- [23] Jianhui L, Rosenblatt-Velin N, Loukili N, et al. Endotoxin impairs cardiac hemodynamics by affecting loading conditions but not by reducing cardiac inotropism. *Am J Physiol Heart Circ Physiol* 2010; 299:H492-501.
- [24] Finkel MS, Oddis CV, Jacob TD, Watkins SC, Hattler BG, Simmons RL. Negative inotropic effects of cytokines on the heart mediated by nitric oxide. *Science* 1992; 257:387-389.
- [25] Walley KR, Hebert PC, Wakai Y, Wilcox PG, Road JD, Cooper DJ. Decrease in left ventricular contractility after tumor necrosis factor-alpha infusion in dogs. *J Appl Physiol* 1994; 76:1060-1067.
- [26] Ronco C, Chionh CY, Haapio M, Anavekar NS, House A, Bellomo R. The cardiorenal syndrome. *Blood Purif* 2009; 27:114-126.
- [27] Breidhardt T, Christ-Crain M, Stolz D, et al. A combined cardiorenal assessment for the prediction of acute kidney injury in lower respiratory tract infections. *Am J Med* 2012; 125:168-175.
- [28] Shor R, Rozenman Y, Bolshinsky A, et al. BNP in septic patients without systolic myocardial dysfunction. *Eur J Intern Med* 2006; 17:536-540.

- [29] Ma KK, Ogawa T, de Bold AJ. Selective upregulation of cardiac brain natriuretic peptide at the transcriptional and translational levels by pro-inflammatory cytokines and by conditioned medium derived from mixed lymphocyte reactions via p38 MAP kinase. *J Mol Cell Cardiol* 2004; 36:505-513.
- [30] Tomaru Ki K, Arai M, Yokoyama T, et al. Transcriptional activation of the BNP gene by lipopolysaccharide is mediated through GATA elements in neonatal rat cardiac myocytes. *J Mol Cell Cardiol* 2002; 34:649-659.
- [31] McCullough PA, Duc P, Omland T, et al. B-type natriuretic peptide and renal function in the diagnosis of heart failure: an analysis from the Breathing Not Properly Multinational Study. *Am J Kidney Dis* 2003; 41:571-579.
- [32] Breidthardt T, Socrates T, Noveanu M, et al. Effect and clinical prediction of worsening renal function in acute decompensated heart failure. *Am J Cardiol* 2011; 107:730-735.
- [33] Franz M, Woloszczuk W, Horl WH. Plasma concentration and urinary excretion of N-terminal proatrial natriuretic peptides in patients with kidney diseases. *Kidney Int* 2001; 59:1928-1934.
- [34] Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med* 2008; 358:125-139.
- [35] Nigwekar SU, Navaneethan SD, Parikh CR, Hix JK. Atrial natriuretic peptide for preventing and treating acute kidney injury. *Cochrane Database Syst Rev* 2009:CD006028.
- [36] Mehta RL, McDonald B, Gabbai F, et al. Nephrology consultation in acute renal failure: does timing matter? *Am J Med* 2002; 113:456-461.
- [37] Shapiro NI, Trzeciak S, Hollander JE, et al. The diagnostic accuracy of plasma neutrophil gelatinase-associated lipocalin in the prediction of acute kidney injury in

emergency department patients with suspected sepsis. *Ann Emerg Med*; 56:52-59
e51.

[38] Pereira M, Azevedo A, Severo M, Barros H. Long-term stability of endogenous B-type natriuretic peptide after storage at -20 degrees C or -80 degrees C. *Clin Chem Lab Med* 2008; 46:1171-1174.

Table 1. Patient's characteristics and clinical outcome

	All patients	No AKI	AKI
Number of patients – n (%)	341	317 (92.4)	24 (7.6)
Age – years	72 [63-82]	75 [64-82]	80 [71-86]
Male – n (%)	209 (61)	196 (62)	12 (50)
Disease severity			
PSI points	103 [80-128]	102 [80-128]	117 [101-148]
CURB-65 points	2 [1-2]	2 [1-2]	2 [1-2]
Comorbidities– n (%)			
Known chronic kidney disease – n (%)	95 (28)	80 (25)	15 (63)
Congestive heart failure – n (%)	39 (11)	36 (11)	3 (13)
Coronary artery disease – n (%)	103 (30)	94 (30)	9 (38)
Cerebrovascular disease – n (%)	24 (7)	24 (7.6)	0 (0)
Hypertensive heart disease – n (%)	82 (24)	72 (23)	10 (48)
Neoplasia – n (%)	63 (18)	59 (19)	4 (17)
Diabetes mellitus – n (%)	69 (20)	62 (20)	7 (29)
Vital status			
Systolic blood pressure (mm Hg)	132 [114-144]	130 [114-144]	134 [113-153]
Heart rate (beats/min)	97 [82-111]	98 [80-110]	98 [80-110]
Respiratory rate (breaths/min)	24 [20-28]	24 [20-28]	22 [20-28]

Body temperature (°C)	38.3 [37.5-39.1]	38.2 [37.5-39.1]	38.3 [37.4-38.7]
Oxygen saturation (%)	92 [89-96]	93 [89-96]	91 [87-96]
Laboratory values			
Creatinine (μmol/L)	104 [80-143]	100 [78-134]	166 [131-289]
Outcome			
Days in hospital – n (%)	14 [8-18]	13 [8-17]	16 [8-21]
ICU/HDU requirement	26 (7.6)	25 (7.9)	5 (21)
30d-mortality – n (%)	38 (11)	32 (10)	6 (25)
Mortality during follow-up – n (%)	154 (45)	137 (43)	17 (68)
Antibiotic treatment			
Patients treated - n (%)	320 (94)	296 (94)	24 (100)
Patients appropriately treated - n (% of all treated)	310 (91)	286 (90)	24 (100)
Antibiotic groups			
Penicillin	253	235	18
Cephalosporin	84	80	4
Macrolide	129	120	9
Carbapenem	8	8	0
Gyrase inhibitor	21	18	3

Others*	9	1	8
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Legend. AKI, acute kidney injury; ICU, Intensive Care Unit; HDU high dependency

Unit

*Others=4xAminoglycosides; 2xThrimetoprin/Sulfomethoxazol; 1xRifampicine;

1xClindamycine; 1xVancomycine

Table 2. Prediction of acute kidney injury development in logistic regression analysis

Predictor	OR	p-value
Univariate logistic regression using base set* variables and NPs		
NT-proBNP ¹	1.01 (1.01-1.02)	<0.001
MR-proANP ²	1.29 (1.17-1.43)	<0.001
BNP ³	1.09 (1.05-1.14)	<0.001
Creatinine ⁴	1.01 (1.00-1.01)	<0.001
CKD	4.94 (2.08-11.72)	<0.001
PSI ⁵	1.01 (1.00-1.02)	0.03
Multivariate logistic regression using base set and NT-proBNP		
NT-proBNP ¹	1.01 (1.00-1.01)	0.009
Creatinine ²	1.00 (1.00-1.01)	0.07
CKD	1.92 (0.65-5.66)	0.24
PSI ⁵	1.00 (0.99-1.02)	0.72

* base set: serum creatinine, chronic kidney disease, pneumonia severity

Legend: NT-proBNP, N-terminal pro brain natriuretic peptide; MR-proANP, midregional-pro atrial natriuretic peptide; BNP, brain natriuretic peptide; PSI, Pneumonia Severity Index

¹ increase of 200 pg/ml

² increase of 100 pmol/L

³ increase of 100 pg/ml

⁴ increase of 1 $\mu\text{mol/L}$

⁵ for each point

Table 3. Prediction of acute kidney injury development in patients with community acquired pneumonia. Area under the curve of receiver operating curve characteristic (ROC) plot analysis

Predictor	AUC	95% CI	P comparison
A. Prediction by single biomarkers			
NT-proBNP	0.79	0.70-0.88	-
MR-proANP	0.78	0.67-0.88	0.9
Creatinine	0.77	0.66-0.88	0.59
BNP	0.74	0.63-0.85	0.27
B. Prediction by models: base set* and NPs			
Base set	0.75	0.63-0.86	-
Base set and MR-proANP	0.78	0.67-0.88	0.28
Base set and NT-proBNP	0.76	0.65-0.88	0.16
Base set and BNP	0.76	0.64-0.87	0.55
C. Prediction by three NPs model versus single base set variables			
Three NPs	0.79	0.69-0.89	-
Creatinine	0.77	0.66-0.88	0.44
CKD	0.69	0.57-0.80	0.003
PSI	0.64	0.53-0.74	0.001

* base set: serum creatinine, chronic kidney disease, Pneumonia severity

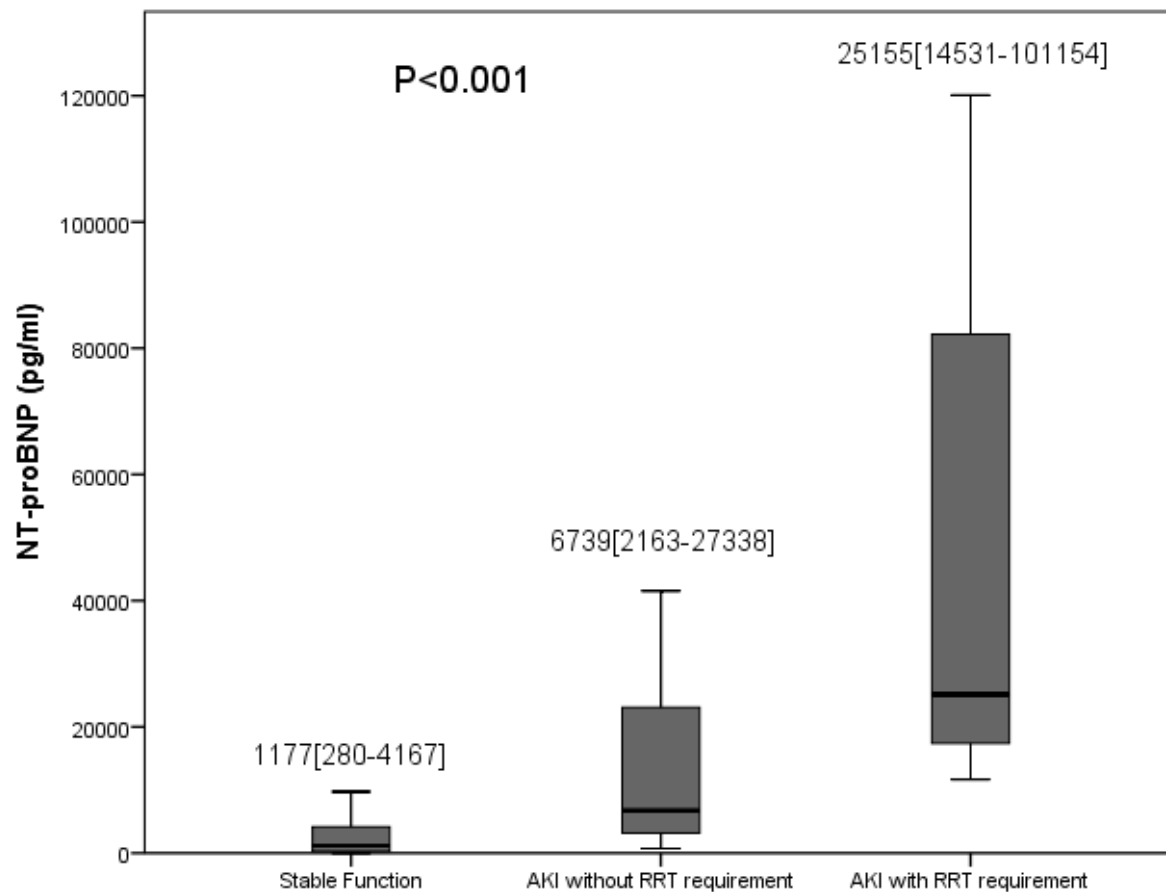
Legend. AUC, area under the curve; SD, standard deviation; CI, confidence interval;
NT-proBNP, N-terminal pro brain natriuretic peptide; MR-proANP, midregional-pro
atrial natriuretic peptide; BNP, brain natriuretic peptide; CKD, chronic kidney disease;
PSI, Pneumonia severity Index

Figure legends

Figure 1. Box plots showing NT-proBNP levels at presentation in patients with stable kidney function (n=317), acute kidney injury without renal replacement requirement (n=19) and with acute kidney injury with renal replacement requirement (n=5).

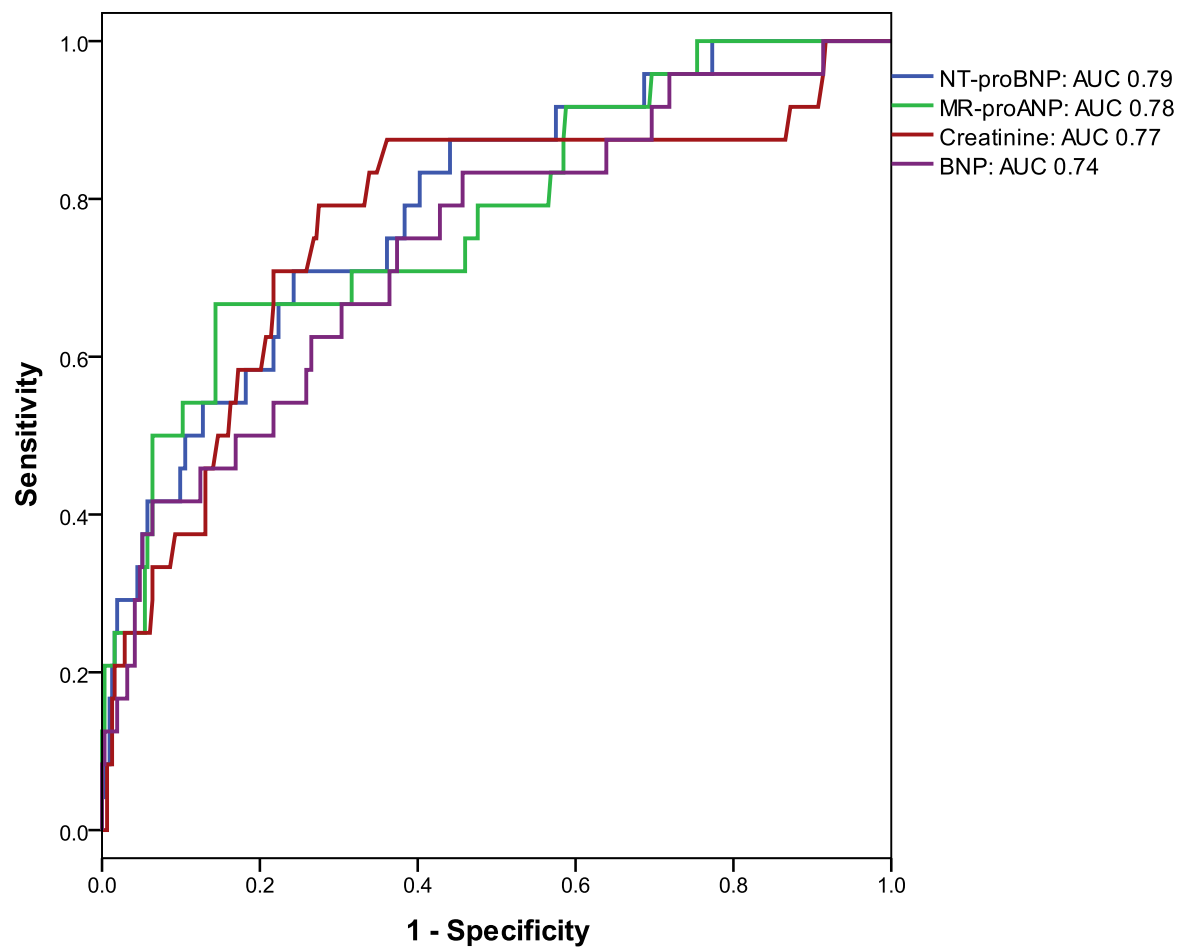
Figure 2. Prognostic accuracy of NT-proBNP, MR-proANP, BNP, and eGFR to predict AKI.

Figure 1. Box plots showing NT-proBNP levels at presentation in patients with stable kidney function (n=317), acute kidney injury without renal replacement requirement (n=19) and with acute kidney injury with renal replacement requirement (n=5).



Legend. AKI, acute kidney injury; eGFR, estimated glomerular filtration rate, NT-proBNP, N-terminal pro brain natriuretic peptide; RRT, renal replacement therapy.

Figure 2. Prognostic accuracy of NT-proBNP, MR-proANP, BNP, and creatinine to predict AKI



Legend. AKI, acute kidney injury; NT-proBNP, N-terminal pro brain natriuretic peptide; MR-proANP, midregional-pro atrial natriuretic peptide; BNP, brain natriuretic peptide